REMARKS/ARGUMENTS

Reconsideration of this application, as presently amended, is respectfully requested.

In view of the final Official action of March 8, 2007, Applicants are respectfully filing a Request for Continued Examination (RCE) and the RCE fee set forth in 37 C.F.R. § 1.17(e) along with the fee pursuant to 37 C.F.R. § 1.136(a) and 37 C.F.R. § 1.17(a)(1) for a one-month extension of time within which to file the RCE by July 9, 2007 (July 8, 2007 falls on a Sunday). All applicable fees are being paid by charge to a deposit account in items 3(a)(i) and 3(a)(ii) of the accompanying Transmittal Form PTO/SB/30 in due time after final rejection. Moreover, the present amendment meets the submission requirements of 37 C.F.R. § 1.114(c) and the reply requirements of 37 C.F.R. § 1.111. Since the application is eligible for continued examination under the provisions of 37 C.F.R. § 1.114, the submission requirements are satisfied and the statutory fees are timely paid, Applicants respectfully ask that the finality of the Office action of March 8, 2007 be withdrawn, the present submission be entered and further examination of the application be undertaken on the basis of the current amendment to the claims.

Regarding the final Office action, the Examiner stressed from page 5 to page 7 that Applicants failed to provide evidence supporting their assertion of unexpected results; Applicants have the burden to establish results are unexpected and significant; and attorney arguments cannot take the place of evidence supported by an appropriate affidavit or declaration having statements of unexpected results. With this in mind, the undersigned attorney contacted the Examiner to determine if she would accept a declaration after the final rejection that would supply the attorney arguments of record in declaration form as per her stipulation stated only in the final rejection. The Examiner kindly explained that the Office would not consider the declaration after final at which time it was agreed that the declaration could be deemed acceptable with the filing of an RCE. To expedite prosecution towards allowance of the application, therefore, the present submission under 37 C.F.R. § 1.114(c) is being promptly filed in lieu of an after final response and includes the accompanying declaration for the Examiner's consideration thereof.

The Examiner maintains the following three rejections for reasons of record: (1) Rejection of Claims 22 and 23 under § 103(a) as being unpatentable over Doyle *et al.* (U.S.

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Patent No. 5,965,128) in view of Clancy *et al.* (U.S. 2004/0057965 A1) and further in view of the Sigma Catalog (Biochemicals and Reagents for Life Science Research, 2000-2001, Adjuvants, page 1472); (2) rejection of Claims 22 (which is believed to be an error as explained below) and 23 under § 103(a) as being unpatentable over Doyle *et al.* (U.S. Patent No. 5,965,128) in view of Clancy *et al.* (U.S. 2004/0057965 A1) and further in view of the Sigma Catalog (Biochemicals and Reagents for Life Science Research, 2000-2001, Adjuvants, page 1472) and further in view of Molly *et al.* (U.S. 2005/0084500 A1); and (3) rejection of Claim 22 under § 103(a) as being unpatentable over Johnson *et al.* ("Effect of vaccination of dairy calves with an inactivated *E. coli* O157:H7 bacterin on shedding of E. coli O157:H7," Food and Environmental Safety Posters, 1999, Abstract 40aP) in view of the Sigma Catalog (Biochemicals and Reagents for Life Science Research, 2000-2001, Adjuvants, page 1472).

Claim 22, as amended, is drawn to a unique method for reducing the shedding of *E. coli* O157:H7 in an animal through the administration by injection of a vaccine composition containing the whole cells of inactivated or killed *E. coli* O157:H7 in admixture with a metabolizable oil adjuvant with the optional inclusion of a pharmaceutically acceptable carrier. Dependent Claim 23 is drawn to a method for reducing the shedding of *E. coli* O157:H7 that provides additionally administering *Lactobacillus acidophilus* or a neomycin medicated feed supplement to the animal being vaccinated. Newly added dependent Claim 24 is directed to the method for reducing the shedding of *E. coli* O157:H7 wherein the claim-recited method specifically and distinctively achieves the reduction of shedding with minimal injection site reactions. Support for the claim is found in the specification on page 4, lines 3-8.

Clarification of the above-noted second rejection is respectfully requested. The earlier rejection of record further applying the cited reference of Molly *et al.* did not include Claim 22. Since Claim 22 does not comprise administering a neomycin medicated feed supplement to animals as the Examiner contends in the middle of page 9 of the last Office action, the inclusion of Claim 22 in this particular rejection is believed to be an error. The present response will proceed under that assumption pending the Examiner's kind verification thereof.

Turning to the merits of the case, Applicants respectfully traverse the rejections of record since the facts do not justify refusal of the present application. To establish a *prima facie*

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case of obviousness, the guidelines of M.P.E.P. § 706.02(j) and case law provide three basic criteria: (1) There must be some suggestion or motivation to modify the reference or to combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) the combined references must teach or suggest all claim limitations. The guidelines of M.P.E.P. § 716.02(a) indicate that a *prima facie* case of obviousness can be rebutted by evidence of results that are unexpected and significant, *i.e.*, the results are greater than those that would have been expected from the art to an unobvious extent and the results are of a significant, practical advantage.

In the case at hand, the *prima facie* case of obviousness is not established because the combined art fails to meet all three factors. More specifically, the real weakness of the rejections of record is two-fold. First and foremost, the rejections are improperly based on cited references that cannot be combined. In other words, there is no motivation or desirability in the art itself to combine or modify the references and arrive at the claimed invention. Secondly, examining exactly what the collective art fairly teaches to the ordinary practitioner, it is clear that the practitioner could not determine the instant claim limitations without inventive effort. Particularly in view of the negative teachings of Doyle *et al.*, the practitioner would be discouraged from finding an injectable formulation for reducing shedding of *E. coli* O157:H7 in cattle. Indeed, the combined art totally fails to provide any suggestion of doing what the inventors have done.

Moreover, there is objective evidence that refutes any contention of *prima facie* obviousness. As proof of non-obviousness, the Examiner's attention is respectfully drawn to the accompanying declaration statements of the inventor, Dr. Wumin Li. The experimental data provide a side-by-side comparison of the novel formulation of the present invention with a typical veterinary vaccine formulation commonly used for bacterial antigens. The results demonstrate that the method of the present invention provides beneficial and unexpected results over those of a conventional formulation.

The showing of better benefits and practical advantages of the unique metabolizable oil adjuvant in Applicants' vaccine composition is surprising in view of the state of the art. Quite unexpectedly, the vaccine formulation of the invention provided the greatest overall serological

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titers and the best improvements in immunity; and, equally surprising under the circumstances, the animals displayed minimal, normal reactions at the vaccine administration sites.

As previously explained in the record, it was not anticipated that the vaccine of the invention would be safe on administration. With all vaccinations, a little lump is expected when the active ingredient is released slowly from the site of depot administration. Typically, vaccines that give a higher immune response cause a greater reaction. Because a severe lump develops from vaccines with significantly higher immunogenic responses, it was initially thought that the claimed vaccine composition would cause a greater adverse reaction. These larger injection site reactions adversely impact the meat quality of an animal which is sold for food consumption and, thus, are an undesirable side effect of potent vaccines. Under the circumstances, therefore, it could not be predicted that the size of the reaction lump of the vaccine of the invention would be the same as the traditional vaccine and no major reaction would be observed. Despite the higher immune response, the results unexpectedly demonstrated that the vaccine containing the metabolizable oil was safe for administration to cattle. The formulation of the present invention is uniquely able to achieve both highly desirable goals of effective immunization and safety, with minimal injection site reactions that would be deleterious to meat quality.

The benefits of Applicants' vaccine formulation to infuse active immunity in the cattle against shedding and to obtain strong antibody titers that prevent colonization of the *E. coli* O157:H7 plus provide bactericidal effect are neither taught nor suggested in the collective art. Such unexpected benefits directly overcome the rejection of Claims 22 and 23 under § 103(a) as being unpatentable over Doyle *et al.* in view of Clancy *et al.* and further in view of the Sigma Catalog, and the rejection of Claim 23 under § 103(a) as being unpatentable over Doyle *et al.* in view of Clancy *et al.* and further in view of the Sigma Catalog, and then further in view of Molly *et al.* for the plain and simple reason that the primary reference of Doyle *et al.* teaches away from the claimed invention.

M.P.E.P. § 2141.02 (prior art must be considered in its entirety, including disclosures that teach away from the claims) and M.P.E.P. § 2146 (references cannot be combined where reference teaches away from their combination) make it clear that negative teachings must be

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considered by the Examiner. It then becomes improper to combine the cited references where the primary reference of Doyle *et al.* teaches away from use of an injectable formulation of *E. coli.*

Doyle *et al.* teach the administration of dominant probiotic bacteria, namely, the specific strains of *E. coli* 271, *E. coli* 786 and *E. coli* 797, to a ruminant animal to prevent and treat the carriage of *E. coli* O157:H7. Patentees indicate that animals known to be shedding *E. coli* O157:H7 in feces are suitable candidates for treatment with their dominant probiotic bacteria (see col. 5, lines 62-65). Doyle *et al.* suggest that feeding non-pathogenic probiotic bacteria to cattle reduces the carriage of the harmful *E. coli* O157:H7 bacteria as a consequence of the competition in the rumen of the animal. However, Doyle *et al.* do not imply that probiotic bacteria can act in any way, shape or form as an injectable vaccine to reduce shedding.

Indeed, Doyle *et al.* expressly teach: "Vaccines are not likely to be effective in reducing the amount of *E. coli* O157:H7 carried and shed by cattle" (col. 2, lines 2-3). Although Doyle *et al.* say that vaccination has been the traditional approach to protecting cattle from carriage of harmful bacteria, they explain that there is difficulty in vaccinating cattle against *E. coli* O157:H7 because the strain does not adhere to or attach to colon tissue and does not infect cattle. As a consequence, Doyle *et al.* use the non-pathogenic dominant probiotic bacteria to reduce localization of *E. coli* O157:H7 in the rumen since they believe that the rumen is the most important site for long-term carriage of *E. coli* O157:H7, and may serve as the source of bacteria found in the colon.

In effect, Doyle *et al.* provide a negative teaching away from Applicants' method for reducing shedding that is uniquely achieved through vaccination of cattle. Based on Doyle *et al.*, there is absolutely no question that one of ordinary skill in the art would be deterred from vaccinating cattle and accomplishing what Applicants have done. The practitioner would have no reasonable expectation of success in reducing shedding of *E. coli* O157:H7 through the administration of Applicants' vaccine composition and the stimulation of a strong immune response. It is quite unexpected, therefore, that Applicants demonstrated a significant reduction of pathogen prevalence in the hide and fecal samples of vaccinated cattle (see, for example, the working Example 3 on page 13 of the application).

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In light of the negative teaching of Doyle *et al.*, there is no reason in the art to motivate the practitioner to modify the teachings sufficiently to arrive at the claimed method. As a further consequence in accord with the guidelines of M.P.E.P. § 2146, it is improper to combine the cited references due to the explicit teaching in the primary reference.

None of the remaining cited art can salvage the improper combination. Clancy *et al.* relate specifically to compositions and vaccines useful for prophylactic or therapeutic treatment of mucosal infections in the respiratory tract. The mucosally administrable composition of Clancy *et al.* comprise one or more antigens derived from at least one microorganism which is capable of causing an infection at a mucosal surface and a probiotic. The reference teaches that the antigen is derived from a bacterium, a fungus or a virus, but only describes those antigens that are respiratory tract pathogens, *i.e.*, those that normally colonize the respiratory tract (specifically, NTHi, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Staphylococcus albus* and *Staphylococcus aureus*).

Although the reference broadly suggests that the vaccine makes use of any mucosal pathogen, Clancy *et al.* purely teach respiratory tract vaccines, showing, for example, the immunization of rats against non-typeable *H. influenzae* (NTHi) by an intra-lumenal (IL) injection (into the lumen of the small intestine). Clancy *et al.* do not describe, exemplify or suggest any antigens that colonize the intestinal tract, let alone *E. coli* O157:H7. Besides, Doyle *et al.* explicitly state that *E. coli* O157:H7 does not adhere to or attach to colon tissue; and it is well known that *E. coli* O157:H7 does not infect cattle. As such, there is absolutely no scientific reason to predict that the mucosally administrable composition of Clancy *et al.* could work with the whole cells of inactivated or killed *E. coli* O157:H7 to reduce shedding in the feces of cattle.

The reference to the Sigma catalog also fails to suggest the present invention. Page 1472 of the Sigma catalog merely shows that a metabolizable oil (squalene) is commercially available as one of three components in the TiterMax Gold and Classic Adjuvants consisting of a block copolymer, squalene and a sorbitan monooleate (Gold Adjuvant) or a block copolymer, squalene and a microparticulate stabilizer (Classic Adjuvant). A generic list of adjuvants from one chemical supplier's catalog does not provide any teaching of which particular adjuvant can

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be used in concert with which antigen for what results. The sheer number of adjuvants that are commercially available from different sources is enormous. Without some direction as to exact combinations, a long list of adjuvants does not describe Applicants' claimed composition or vaccine of an injectable *E. coli* O157:H7. The only reason one would be motivated to find a metabolizable oil on this specific page of the Sigma catalog would be through impermissible hindsight vision, having the claimed invention already at hand. The pure fact that the ordinary practitioner needs to pick and choose among a huge variety of options means that the reference does not render the present invention obvious.

Taking the invention as a whole and examining the cited references in their entirety, it is clear that one of ordinary skill in the art would not arrive at the claimed invention from the teachings of the combined references. First of all, Doyle *et al.* and Clancy *et al.* do not teach methods for reducing the shedding of *E. coli* O157:H7 in an animal through active immunity, *i.e.*, inoculating cattle with an effective vaccine composition. Secondly, it cannot be inferred from either of these two references that a vaccine containing inactivated or killed whole cells of *E. coli* O157:H7 would work against *E. coli* O157:H7. Based on the negative teachings of Doyle *et al.* and the limited respiratory tract vaccine of Clancy *et al.*, the practitioner could not anticipate being able to achieve a superior immune response to the vaccine formulation comprising whole cells of *E. coli* O157:H7 and a metabolizable oil adjuvant. The combined references simply fail to teach or suggest all claim limitations of Applicants' method of Claim 22.

Insofar as Claim 23 is concerned, the collective art in further view of Molly *et al.* do not suggest the claimed invention. Molly *et al.* relate to a growth promoter composition suitable for animals that comprises a fungus and at least one growth-promoting component comprising organic acids, inorganic acids, animal feed antibiotics, conventional growth promoters or plant extracts. The fungus, which is a critical component of the growth promoter composition, is never omitted from any composition described by Molly *et al.* While they disclose that one aspect of their invention involves feeding the growth promoter composition to an animal and inducing changes in the microbial ecosystem in the gastrointestinal tract of the animal, this method for improving the gastrointestinal tract would mandate that the entire composition be given to the animal, including the fungus taught by Molly *et al.* as an essential feature.

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Although the reference generically discloses that an undesired enteric pathogen could be *Escherichia* among a large list of other enteric pathogens and generically identifies neomycin as an animal feed antibiotic that could be added to the fungus of the growth promoter composition, Molly *et al.* purely suggest that neomycin be used in combination with the fungus to improve the gastrointestinal microbial ecosystem by suppressing pathogens in the gastrointestinal tract of the animals. However, there are no specific formulations or examples that contain neomycin. Rather, exemplification in Molly *et al.* is limited to showing the influence of *Lentinus edodes* in combination with a growth-promoting component on the growth and feed conversion ratio (FCR) of chickens and pigs.

Additionally, Molly *et al.* indicate that while FCR can be lowered by influencing the bio-regulatory process through administering traditional antimicrobials or feed antibiotics, antibiotic therapy has the disadvantage in that it results in the destruction of the intestinal microflora ([0005]). Reading the entire disclosure, it is plain to see that Molly *et al.* do not promote the use of an animal feed antibiotic such as neomycin in the absence of fungus as it will have an adverse effect on the animal.

Without question, the combined references do not teach or suggest all of the limitations of Claim 23. Neither Doyle *et al.* nor Clancy *et al.* teach a vaccine containing whole cells of *E. coli* O157:H7. There is no suggestion or motivation in either reference to combine their teachings with the Sigma catalog and make a precise selection of only one adjuvant, the metabolizable oil, out of numerous commercially available adjuvants from Sigma and elsewhere. Certainly, Molly *et al.* do not add the motivation to select and use neomycin in combination with a vaccine for reducing shedding of *E. coli* O157:H7. Particularly owing to the negative teachings of Doyle *et al.* and the lack of any basis to expect that the claimed injectable method would be successful in reducing the shedding of *E. coli* O157:H7, this rejection cannot be sustained.

With respect to the last rejection in which Claim 22 is separately rejected under § 103(a) as being unpatentable over Johnson *et al.* in view of the Sigma Catalog, there are a few main reasons why this rejection cannot stand. First of all, the teaching or suggestion to make the claimed vaccine composition comprising, at the very least, inactivated or killed whole *E. coli*

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O157:H7 and a metabolizable oil adjuvant and the reasonable expectation of success must both be found in the prior art, not Applicants' disclosure (*In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)). Under the present circumstances, there is no reason in either Johnson *et al.* or the Sigma Catalog to employ the whole bacteria as the antigen or to select the specific metabolizable oil adjuvant for use with *E. coli* in an injectable vaccine and expect success.

Johnson *et al.* describe inoculating dairy calves with a vaccine containing inactivated *E. coli* O157:H7, inactivated verotoxin 2 and intimin O157, a totally different vaccine composition which does not suggest Applicants' efficacious vaccine formulation. Verotoxin 2 is a known Shiga toxin produced by *E. coli*. The protein is made up of two subunits: one is responsible for toxic action and the other, for binding to a specific cell type. Verotoxin requires highly specific receptors on the host cells' surface to attach and enter the cell. Cattle do not carry these receptors and, consequently, they shed the bacteria in their feces without being infected by the bacteria. Intimin O157, extracted from the outer membrane of *E. coli* O157:H7, is a bacterial protein that permits the *E. coli* to adhere to the host's intestinal cell walls. The bacteria require intimin to colonize their host, attach themselves to intestinal tissue and cause human disease. Much research has been placed on developing vaccines that prevent the transmission of the bacterial protein intimin to the host cell. It makes sense, therefore, that Johnson *et al.* would attempt to use a vaccine that employs intimin O157 along with the Shiga toxin to produce antibodies against *E. coli* O157:H7. Particularly where verotoxin 2 and intimin O157 are art-recognized as vital for bacterial activity, Johnson *et al.* clearly do not teach or propose using the whole cells of *E. coli* O157:H7 in the absence of these two critical components. As such, one of ordinary skill in the art could not predict the immune effect of injecting the whole cells of *E. coli* O157:H7, and omitting verotoxin 2 and intimin O157, without substantial experimentation.

In addition, neither Johnson *et al.* nor the Sigma Catalog describe or suggest the selection of the specific metabolizable oil adjuvant of the claimed method for use with *E. coli* O157:H7. An essential claim limitation comprising the metabolizable oil adjuvant, therefore, is totally missing from the collective art.

Moreover, the rejection cannot stand because the cited references do not suggest the desirability or advantage of the claimed invention, that is, both references are silent in providing

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a potent, immunogenic vaccine that is safened for injectable administration to food animals. In this regard, the declaration demonstrates that the formulation of the present invention elicits a strong immune response yet surprisingly provides a minimal injection site reaction that avoids the anticipated adverse impact on meat quality. The showing of unexpected results clearly refutes any obviousness based on the vaccine of Johnson *et al.* in light of the Sigma Catalog.

In view of the foregoing remarks, the present amendment and the proffered evidence in declaration form, Applicants respectfully request that all of the rejections be withdrawn.

If any outstanding issue remains, the Examiner is invited to contact the undersigned attorney for a discussion of mutually agreeable solutions.

Accordingly, Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

WYETH

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